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09/593,173	06/12/2000	Antonio Guarna	1195-003	5454

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EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 04/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/593,173	GUARNA ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,10 and 27-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,10 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Actions

The Quayle Action at paper no. 19 is withdrawn in light of the new rejections.

Claims 1, -3, 10, 27-29 are pending in the case.

(new objections)

Claim(s) 1 is/are objected to for being substantial duplicate of claims 28and 29. When two claims in an application are duplicates, or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. M.P.E.P. 706.03(k). This objection can be overcome by deleting claim 28.

Claim 1 is objected to because of the following informalities: In line 8, page 2 of the paper filed 1/24/04, the term "canphane" is a misspelling of the term "camphene". Appropriate correction is required.

Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 10, and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

was filed, had possession of the claimed invention. There is not sufficient description of what esters of the compound of formula I are being claimed. In the absence of how to make esters of the compounds of formula I being claimed, there is no umbrella coverage springing forth from the claim compound of formula I and the few examples of esters depicted in the specification. There is also insufficient description for a method of inhibiting 5 alpha reductase-I and/or 5 alpha reductase-II iso-enzymes and the treatment of the diseases claimed to be associated with this enzyme in claim 27. There is also insufficient description of what is meant by the phrase "fully and partially reduced" in line 1 of claims 1, 28, 29. Does this phrase mean that any of the double bonds are reduced? Is there reduction only at the particular position in the compound where the dotted lines are in the compound where there can be double or single bonds?

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention in is the synthesis of benzo[c]-quinolizine derivatives and their use for inhibiting 5- alpha R-1 and 5 alpha R-11 reductase enzymes in order to treat pathologies mediated by the enzyme or for agricultural uses.

The State of the Prior Art

The enzyme known as steroid 5 alpha reductase is a system formed by two iso-enzymes (type I and type II or 5 alpha R-1 and 5 alpha R-11 respectively), which converts testosterone into dihydrotestosterone, the most powerful androgen circulating in the body. The type I iso-enzyme is mainly present in liver and skin while the type II iso-enzyme (5 alpha R-11) is mainly present in liver in the prostate tissue and in the male sexual organs and its activity is essential in the fetal developing process for the differentiation of the external sexual organs. In the recent years, attempts have been made to try to isolate new compounds capable of inhibiting 5 alpha –reductase enzyme in order to treat pathologies associated with the enzyme such as cancer, baldness, hypertrophy, and acne. In EP 703221, EP-591-582, EP – 591-583, EP 532 190, and EP –531 026, benzoquinoline-3-ones as 5 alpha reductase inhibitors have been reported.

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of 5 alpha reductase -mediated

diseases, whether the 5 alpha reductase enzyme was promoted or inhibited would affect the possible treatment of any disease.

Hence, in the absence of a showing of correlation between all the diseases claimed in claim 27 as capable of treatment by the compound of claim 1 and the inhibition of 5 alpha reductase, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of 5 alpha reductase, i.e. whether promotion or inhibition would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present

The direction present in the instant specification is that the compounds of claim 1 can inhibit 5 alpha reductase and treat the diseases claimed in claim 27. However, the specification is silent and fails to provide guidance as to whether the diseases claimed in claim 27 as 5 alpha reductase-mediated diseases, require the inhibition of 5 alpha reductase for treatment, i.e. the specification fails to provide a correlation between the diseases listed and the inhibition of 5 alpha reductase via experimental data. The applicant only provides inhibition assays for the instant compounds on 5 alpha

reductase enzyme; however, does not examine the pharmacological effects of these compounds on any of the diseases claimed in claim 27. The specification does not disclose experimental data of the inhibition assays for a wide variety of the instant compounds being claimed.

The presence or absence of working examples

The compounds which are disclosed in the specification have no pharmacological data regarding the treatment of any disease. Also, the specification fails to provide working examples as to how the disclosed diseases can be treated by the inhibition of 5 alpha reductase enzyme , i.e. again, there is no correlation between the diseases listed and inhibition of 5 alpha reductase enzyme.

The breadth of the claims

The breadth of the claims is that the compound of claim 1 can treat the diseases claimed in claim 27 by inhibiting 5 alpha reductase.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which disclosed diseases would be benefited by the inhibition of 5 alpha reductase enzyme and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the inhibition of 5 alpha reductase enzyme.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be

individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claim 1 for the prevention or treatment of an any disease caused or promoted by the nerve controlling function of a sigma ligand. As a result necessitating one of skill to perform an exhaustive search for which Sigma-mediated diseases can be treated by the compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which 5 alpha reductase enzyme -mediated diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 27, 28, and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, line 10, page 3 of the paper filed 1/28/04, in claim 28, page 11, line 8 of the paper filed 1/28/04 and in claim 29, page 12 of the amendment filed 1/28/04, the phrase "salts and esters" is ambiguous. A compound, by definition, can only contain one compound, not several compounds. Claims 1, 28-29 are contradictory because they are simultaneously claiming a singular "compound" and yet "more than one compound" by claiming "salts and esters". Is the applicant claiming a "compound" or a "mixture" which contains at least two or more compounds? Also, it is not clear as what salts and esters of the compound the applicant is claiming.

B. In claim 1, line13, page 2 of the paper filed 1/28/04, in claim 28, line 13, page 10 of the paper filed 1/28/04, and in claim 29, line 13, page 11, the phrase "wherein R and R' are as above defined" is indefinite and ambiguous, because R and R' are never defined in these claims.

C. Claim 3, line 1, page 3, the phrase "A benzo[c]quinolizine compounds" is indefinite and ambiguous. A compound can only contain one compound, not several compounds. Claim 3 is contradictory because it is a compound claim simultaneously claiming "more than one compound". Is the applicant claiming a "compound" or a "mixture" which contains at least two or more compounds?

D. Claim 3 recites the limitation "compounds" in line 1 of claim 3. There is insufficient antecedent basis for this limitation in the claim.

E. Claim 27 is indefinite and ambiguous because it is not in the proper format for a method of treating claim. There is no reference to the compound being administered in a therapeutically effective amount to a host in need thereof.

F. In claims 1, 28, 29, line 1, of pages 2, 10, and 11, the phrase "fully and partially reduced" is ambigous. Does this phrase mean that any of the double bonds are reduced? Is there reduction only at the particular position in the compound where the dotted lines are in the compound where there can be double or single bonds?

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim(s) 1, 2, 28, 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Acheson et. al. (See Reference U). Acheson discloses the instant compound, 8. At page 584 , see the instant compound. It is assumed that the Acheson compound upon reduction will be the instantly claimed compound.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 28, 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 6514912 in view of Guarna (J. Med. Chem. 1997, Vol. 40, pages 1117 especially) and Strandtmann et. al. (J. Org. Chem., March 1966, 31 (3), 797 especially). Although the conflicting claims are not identical, they are not patentably distinct from each other because US 6514912 patent is claiming benzo[c]quinolizine derivatives for inhibiting 5-alpha –reductase enzymes.

U.S. Patent No. 6514912 et. al. teaches the compound as shown in Formula I, wherein R1, R2, R3, R4 and R6 which are the same or different from one another are chosen from the group consisting of H, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C3-6 cycloalkyl, aryl, halogen, CN, azide, NRR', C18 alkylamine, arylamine, C1-8 alkyloxy, aryloxy, COOR, and CONRR', where R and R', which are the same or different from one another, are chosen from the group consisting of H, C1-8 alkyl, aryl, heterocycle, aryl-C1-8 alkyl, and cycyl-alkyl, X is chosen from the group consisting of O, C(=O)R, COOR, NO2, and CONNR' in which R and R' are as defined above; Q is chosen from the group consisting of single-bond, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, cyclo-alkyl, CO, CONR, and NR, where R is as defined above; W is chosen from the group consisting of H, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, cycloalkyl, trifluoromethyl, C1-8 alkoxy, c1-8 aloxy-C1-8 alkyl, aryl-C1-8 alkyl, aryl , aryloxy, arylamine, C1-8 alkyl-carbonyl, arylcarbonyl, halogen, CN, NRR', C1-8 alkylamine, and heterocycle, n is 1, 2,

3 or 4; the mark ---------- indicates that the respective bonds a, b, c, d, e, f, and g are single or double bounds, considering that when b or f are a double bound, the R5 group is absent, R5 is C1-8 alkyl-aryl or C1-8 alkyl heterocycle , with the proviso that when R5 is benzyl at least one of the R1, R6, X, and R2 is not a COOR group. At column 7, see the compound of formula I in claim 5, where the radicals defined. The difference between the US patent 6514912 compound and the instantly claimed compounds is the teaching of a benzo[c]quinolizine compound where the phenyl moiety of the benzoquinolizine core is fully unsaturated in the US patent 6514912 compound, and only partially unsaturated in the instant compound. Guarna and Strandtmann teach that a fully reduced C ring in an azasteroid core is analogous to a fully unsaturated C ring in a benzoquinolizine core. In the azasteroid ring system, the C ring can be either partially or fully reduced, whereas in the benzoquinolizine core, the C ring is fully unsaturated. In view of Guarna and Strandtmann and since instant the benzo[c]quinolizine compounds have the same function of being able to inhibit 5-alpha –reductase enzymes and are benzo[c]quinolizine derivatives of the US patent 6514912 compounds, it would have been obvious to one of ordinary skill in the art to modify the C ring of a benzo[c]quinolizine compound so that it is partially to fully reduced and to use this compound inhibiting 5-alpha –reductase enzymes. For instance, see claim 6 of US patent 6514912, where a disclosed species is exemplified. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the US patent 6514912 compounds.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 28, and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. US 6303622; Claim 3 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 3 of U.S. Patent No. US 6303622; Claim 27 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6,7, 8, 9, 10, 13 of U.S. Patent No. US 6303622; Claim 10 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 12 of U.S. Patent No. US 6303622 in view of Guarna (J. Med. Chem. 1997, Vol. 40, pages 1117 especially) and Strandtmann et. al. (J. Org. Chem., March 1966, 31 (3), 797 especially). Although the conflicting claims are not identical, they are not patentably distinct from each other because, US 6303622 patent is claiming benzo[c]quinolizine derivatives; pharmaceutical compositions containing such derivatives; methods of treating acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism and a method

for inhibiting 5-alpha –reductase enzymes by administering an effective amount of these benzo[c]quinolizine derivatives.

U.S. Patent No. 6303622 et. al. teaches the benzo[c]quinolizine compounds as shown in Formula I, methods of treating acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism and a method for inhibiting 5-alpha –reductase enzymes by administering an effective amount of these benzo[c]quinolizine derivatives. At column 8, see the compound of formula I, where the radicals defined, and see claims 6 and 7 at column 8, claims 8-10, at column 9 and claims 12-13 at column 10. The difference between the US patent 6303622 compound, pharmaceutical composition, and method of treating acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism and inhibiting 5-alpha –reductase enzymes by administering an effective amount of these benzo[c]quinolizine derivatives and the instantly claimed compounds is the teaching of a benzo[c]quinolizine compound where the phenyl moiety of the benzoquinolizine core is fully unsaturated in the US patent 6303622 compound, and only partially unsaturated in the instant compound and pharmaceutical compositions comprising such compounds, and a method of inhibiting 5-alpha –reductase enzymes, and treating acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism using such compounds. Guarna and Strandtmann teach that a fully reduced C ring in an azasteroid core is analogous to a fully unsaturated C ring in a benzoquinolizine core. In the azasteroid ring system, the C ring can be partially to fully reduced, whereas in the benzoquinolizine core, the C ring is fully unsaturated. In view of Guarna and Strandtmann and since the benzo[c]quinolizine compounds have the same function of being able to inhibit 5-alpha

–reductase enzymes, and treat acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism, it would have been obvious to one of ordinary skill in the art to modify a benzo[c]quinolizine compound so that the phenyl moiety of the benzo[c]quinolizine core is partially unsaturated for use in inhibiting 5-alpha –reductase enzymes. For instance, see claims 1, 2, 4, 6, 7-10, 12, 13 at columns 8-10. Accordingly, the instant compounds, pharmaceutical compositions, and method of treating are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds, pharmaceutical compositions, and a method of treating over those of the US patent 6303622 compounds, pharmaceutical compositions, and a method of treating.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 28, 27, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna (see Reference N) in view of Guarna (J. Med. Chem. 1997, Vol. 40, pages 1117 especially) and Strandtmann et. al. (J. Org. Chem., March 1966, 31 (3), 797 especially).

Guarna et. al. teaches the benzo[c]quinolizine derivatives as shown in Formula I, where R1-R4, R6 are the same or different, are chosen from the group consisting of: H, C1-8

alkyl, C2-8 alkenyl, C2-8 alkinyl, cycloalkyl, aryl, R5 is chosen from the group consisting of H, C1-8 alkyl, COOR, CN, aryl, X is chosen from O, C(=O)R, COOR, NO2, CONRR', wherein R and R' are H, C1-8 alkyl, cycloalkyl, aryl, arylC1-8 alkyl, Q is chosen from the group consisting of simple bond, C1-8 alkyl, C2-8 alkenyl, C2-8 alkinyl, cycloalkyl, CO, CONR, NR, wherein R is as above defined, W is chosen from the group consisting of H, C1-8 alkyl, C2-8 alkenyl, C2-alkinyl, cycloalkyl, C1-8 alkoxy, C1-8 alkoxy-C1-8 alkyl, arylC1-8alkyl, aryl, aryloxy, arylamino, C1-8 alkylcarbonyl, arylcarbonyl, halogen, CN, NRR', C1-8 alkylamino, n is an integer comprised between 1 and 4, the symbol ------- means that the corresponding bonds, a, b, c, d, e, f and g can be simple or double bonds, with the proviso that when b or f are a double bound, then the group R5 is absent, their pharmaceutically acceptable salts or esters and a method of treating pathologies related to 5 alpha reductase enzymes and for treatment of acne, baldness, prostatic cancer and prostatic hypertrophy in men and hirsutism in women, by administration of the benzo[c]quinolizine compounds. At page 14-15, see claims 1-2, at page 18, see claim 7, claim 8, claims 12, 13.

The difference between the prior art compound, pharmaceutical composition, and method of treating acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism and inhibiting 5-alpha –reductase enzymes by administering an effective amount of these benzo[c]quinolizine derivatives and the instantly claimed compounds, pharmaceutical compositions, and a method of treating acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism and inhibiting 5-alpha –reductase enzymes is the teaching of a benzo[c]quinolizine compound where the phenyl moiety of the benzoquinolizine core is

fully unsaturated in the Guarna compound, and only partially unsaturated in the instant compound, pharmaceutical compositions comprising such compounds, and a method of inhibiting 5-alpha –reductase enzymes, and treating acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism using such compounds. Guarna and Strandtmann teach that a fully reduced C ring in an azasteroid core is analogous to a fully unsaturated C ring in a benzoquinolizine core. In the azasteroid ring system, the C ring can be partially to fully reduced, whereas in the benzoquinolizine core, the C ring is fully unsaturated. In view of Guarna and Strandtmann and since, the benzo[c]quinolizine compounds have the same function of being able to inhibit 5-alpha –reductase enzymes, and treat acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism, and are benzo[c]quinolizine derivatives of the prior art compounds, it would have been obvious to one of ordinary skill in the art to modify a benzo[c]quinolizine compound so that the phenyl moiety of the benzo[c]quinolizine core is partially unsaturated for use in inhibiting 5-alpha –reductase enzymes, for use as pharmaceutical compositions, and for treating acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism . For instance, see claims 1-2, at page 18, see claim 7, claim 8, claims 12, 13 . Accordingly, the instant compounds, pharmaceutical compositions, and method of treating are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds, pharmaceutical compositions, and a method of treating over those of the prior art compounds, pharmaceutical compositions, and a method of treating.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 28, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable Guarna et. al. (WO9905913, See Reference S) in view of Guarna (J. Med. Chem. 1997, Vol. 40, pages 1117 especially) and Strandtmann et. al. (J. Org. Chem., March 1966, 31 (3), 797 especially). Guarna et. al. teaches the compound as shown in Formula I, wherein R1, R2, R3, R4 and R6 which are the same or different from one another are chosen from the group consisting of H, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C3-6 cycloalkyl, aryl, halogen, CN, azide, NRR', C18 alkylamine, arylamine, C1-8 alkyloxy, aryloxy, COOR, and CONRR', where R and R', which are the same or different from one another, are chosen from the group consisting of H, C1-8 alkyl, aryl, heterocycle, aryl-C1-8 alkyl, and cycyl-alkyl, X is chosen from the group consisting of O, C(=O)R, COOR, NO2, and CONNR' in which R and R' are as defined above; Q is chosen from the group consisting of single-bond, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, cyclo-alkyl, CO, CONR, and NR, where R is as defined above; W is chosen from the group consisting of H, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, cycloalkyl, trifluoromethyl, C1-8 alkoxy, c1-8 aloxy-C1-8 alkyl, aryl-C1-8 alkyl, aryl , aryloxy, arylamine, C1-8 alkyl-carbonyl, arylcarbonyl, halogen, CN, NRR', C1-8 alkylamine, and heterocycle, n is 1, 2,

3 or 4; the mark---------- indicates that the respective bonds a, b, c, d, e, f, and g are single or double bounds, considering that when b or f are a double bound, the R5 group is absent, R5 is C1-8 alkyl-aryl or C1-8 alkyl heterocycle , with the proviso that when R5 is benzyl at least one of the R1, R6, X, and R2 is not a COOR group. At page 7, see the compound of formula I in claim 1, where the radicals are defined and see claim 6. The difference between the Guarna compound and the instantly claimed compounds is the teaching of a benzo[c]quinolizine compound where the phenyl moiety of the benzoquinolizine core is fully unsaturated in the Guarna compound, and only partially unsaturated in the instant compound. Guarna and Strandtmann teach that a fully reduced C ring in an azasteroid core is analogous to a fully unsaturated C ring in a benzoquinolizine core. In the azasteroid ring system, the C ring can be partially to fully reduced, whereas in the benzoquinolizine core, the C ring is fully unsaturated. In view of Guarna and Strandtmann and since instant the benzo[c]quinolizine compounds have the same function of being able to inhibit 5-alpha –reductase enzymes and are benzo[c]quinolizine derivatives of the Guarna compounds, it would have been obvious to one of ordinary skill in the art to modify the C ring of a benzo[c]quinolizine compound so that it is partially to fully reduced and to use this compound inhibiting 5-alpha –reductase enzymes. For instance, at page 8, see claim 4 of Guarna, and at page 9, see claim 6, where a disclosed species is exemplified. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the Guarna compounds.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 10, 27, 28, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et. al. (EP 926148, See Reference T) in view of Guarna (J. Med. Chem. 1997, Vol. 40, pages 1117 especially) and Strandtmann et. al. (J. Org. Chem., March 1966, 31 (3), 797 especially). Guarna '148 teaches the benzo[c]quinolizine compounds as shown in Formula I, methods of treating acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism and a method for inhibiting 5-alpha –reductase enzymes by administering an effective amount of these benzo[c]quinolizine derivatives. At pages 11-12, claim 1, see the compound of formula I, where the radicals defined and at page 18, see claims 8, 9, 10, 11, and12. The difference between the Guarna '148 compound, pharmaceutical composition, and method of treating acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism and inhibiting 5-alpha –reductase enzymes by administering an effective amount of these benzo[c]quinolizine derivatives and the instantly claimed compounds is the teaching of a benzo[c]quinolizine compound where the phenyl moiety of the benzoquinolizine core is fully unsaturated in the Guarna compound, and only partially unsaturated in the instant compound and pharmaceutical compositions comprising such compounds, and a

method of inhibiting 5-alpha –reductase enzymes, and treating acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism using such compounds. Guarna and Strandtmann teach that a fully reduced C ring in an azasteroid core is analogous to a fully unsaturated C ring in a benzoquinolizine core. In the azasteroid ring system, the C ring can be partially to fully reduced, whereas in the benzoquinolizine core, the C ring is fully unsaturated. In view of Guarna and Strandtmann and since the benzo[c]quinolizine compounds have the same function of being able to inhibit 5-alpha –reductase enzymes, and treat acne, baldness, prostate cancer, prostatic hypertrophy, hirsutism, it would have been obvious to one of ordinary skill in the art to modify a benzo[c]quinolizine compound so that the phenyl moiety of the benzo[c]quinolizine core is partially unsaturated for use in inhibiting 5-alpha –reductase enzymes. Accordingly, the instant compounds, pharmaceutical compositions, and method of treating are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds, pharmaceutical compositions, and a method of treating over those of the Guarna compounds, pharmaceutical compositions, and a method of treating.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR

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